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Glomerular lesions in aleutian disease of mink *(Mustela vison)*: A morphological and differential morphometrical study

J.M. Nieto, C. Alvarez, J.M. Flores and J. Romano
Department of Animal Pathology, Anatomical Pathology Section, Faculty of Veterinary, Lugo, Spain.

Summary. A morphological and morphometrical study has been carried out on glomerular lesions in mink with spontaneous Aleutian disease, using the WHO classification for Systemic Lupus Erytematous Nefritis. 154 renal samples from sick animals and 10 samples from uninfected mink were processed by routine histopathological techniques and metacrylate inclusions. The samples were studied quantitatively with an automatic image analyzer. 5 forms of glomerulonephritis (GN) were identified: mesangial glomerulonephritis (n = 13), focal and segmental GN (n = 10), diffuse GN (n = 99), membranous GN (n = 12) and advanced sclerosing GN (n = 10) and were associated with the degree of interstitial plasmocytosis. Glomerule morphometry was shown to be an excellent method for identifying the type of lesion, while it quantified the participation of various glomerular elements in the lesion.

Key words: Aleutian disease, Glomerulonefritis, Morphopathology, Morphometry

Introduction

Aleutian Disease (AD) of mink is a persistent virus infection caused by a virus of the Parvoviridae family (Aasted, 1980; Bloom et al., 1980) that causes systemic plasmocytosis accompanied by a marked increase in the seric gammaglobulins (Lodmel and Portis, 1981; Porter et al., 1984), proteinuria (Trautwein et al., 1969) and uraemia (Gershbsein and Spencer, 1964). The disease may affect all the varietes of mink, but is particularly grave in recessive homozygotic animals of the aleutian gen (Johnson et al., 1975).

Morphologically, AD is characterized by systemic plasmocytosis that mainly affects the bone marrow, spleen, lymph nodes, liver and kidneys (Obel, 1971; Trautwein, 1970), together with other lesions induced by the deposit of immunocomplexes: uveitis (Hadlow, 1982), glomerulonephritis (GN) (Kastard, 1965; Henson et al., 1968, 1969; Johnson, 1975; Muller-Peddinhaus and Trautwein, 1983) and necrotizing arteritis (Porter et al., 1973). Neonatal infection due to the AD virus causes a different form of disease characterized by interstitial pneumonia (Alexandersen and Bloom, 1986).

Glomerular lesions occurring during the course of AD have been described by various authors and proposed as a comparative study model for Systemic Lupus Erytematous nephritis (LES) (Muller-Peddinhaus and Trautwein, 1983).

The aim of our work was to morphologically and morphometrically analyze the various types of glomerulonephritis developed in spontaneous AD, classifying them according to the standards suggested by the WHO for Systemic Lupus Erytematous nephritis (Churg and Sobin, 1982).

Materials and methods

Animals

The study was carried out with 154 minks of both sexes and aged between 2 and a half months and twelve months. All the animals came from the same farm. 144 animals showed diagnosed AD through clinical, pathological and counter-electroimmunophoresis (CEIP): 137 died spontaneously, due to the disease, the remaining 7 were sacrificed during the terminal phases of AD. 10 animals —negative under the CEIP test— were selected as controls. 72 animals belonged to the Wild variety and 82 to the Standard variety.

Histopathological technique

Samples for routine histopathological studies were

Offprint requests to: Dr. J.M. Nieto, Departamento de Patología Animal, Unidad de Anatomía Patológica, Facultad de Veterinaria, E-27002 Lugo, Spain

fixed in 4% formalin (24 h) and later in 10% formalin. They were embedded in paraplast, and 4 μm thin sections were stained with H-E, PAS and silver-methenamine techniques.

Other samples were embedded in 2-hydroxyethyl-metacrylate (Technovit 700), after fixing in formalin according to the technique described above and after dehydrating in 70% alcohol (2 h) and later at 95% (2 h). The inclusion on metacrylate was carried out in two stages - inclusion in monomer I (12 h, ambient temperature) and later hardening (1 h, 37° C)-. 1 μm thin sections were obtained and stained with silver-methenamine method.

Quantitative analysis

One observer carried out the morphometric analysis of the samples included in 2-hydroxyethyl-metacrylate, evaluating the following parameters: 1) total glomerular area; 2) surface of the mesangial area; 3) number of epithelial cells/glomerule; 4) number of endothelial cells/glomerule; 5) number of mesangial cells/glomerule; 6) total number of cells/glomerule; 7) number of mesangial cells/1000 μm^2 of mesangial area, 8) number of glomerular cells/100 μm^2 of glomerule area.

All the analyses were carried out with the aid of a VIDSM II automatic image analyzer loaded with «General Area» software. Quantitative determinations were carried out on 40 renal samples: 10 from normal animals and 30 with panglomerular lesions (10 Mes GN, 10 Dif GN, 5 Mem GN, 5 Ad, GN). To carry out the quantitative analysis samples with focal glomerular lesions were excluded; the glomeruly selected were of short nephrons.

In order to check the objectivity of the results, 50% of the samples were analyzed by another observer. The repetivity test was realized through the analysis of 50% samples by the same observer who had evaluated all of the renal samples.

For the comparative study of the results the «t» Student test was used.

Results

The histopathological study of the samples revealed the existence of five main forms of GN. Table 1 shows the incidence of the different types in relation to age and variety. According to the WHO classification, lesions were considered to be focal when alterations affected less than 80% of the glomerules, and diffuse when the number of affected glomerules was greater. The term segmental lesion is used to determinate those alterations that affect part of the glomerule; the denomination global lesion is used to identify lesions that uniformly affect the glomerule.

Mesangial Glomerulonephritis (Mes GN)

Mes GN was identified in 13 animals. The lesion consisted of moderate enlargement of the mesangial space, due to either to the increase in the number of mesangial cells (10 cases) or to the depositing of argentophilic material in the amorphal matrix of the mesangium (3 cases) (Fig. 1). Frequently, mixtures of both alterations were found, with one lesion or the other predominating.

Interstitial plasmocytosis associated with this form of GN was moderate and localized mainly in peri-vascular areas (Table 2).

Focal and segmental Glomerulonephritis (F/S GN)

10 animals showed focal and segmental lesions, consisting of sclerosis of the mesangial area (2 cases), proliferation of mesangial cells (5 cases) (Fig. 2) and partial necrosis of the vascular turf (3 cases).

Sclerosis lesions were identified by the deposition of argentophilic material in the mesangial space, mainly in the distal regions of the capillary turf (4 cases); in one animal the proliferation was located in the vascular pole.

Fig. 1. Mesangial glomerulonephritis (Mes GN). Moderate enlargement of the mesangial space due to the depositing of argentophilic material. Silver-methenamine. × 600

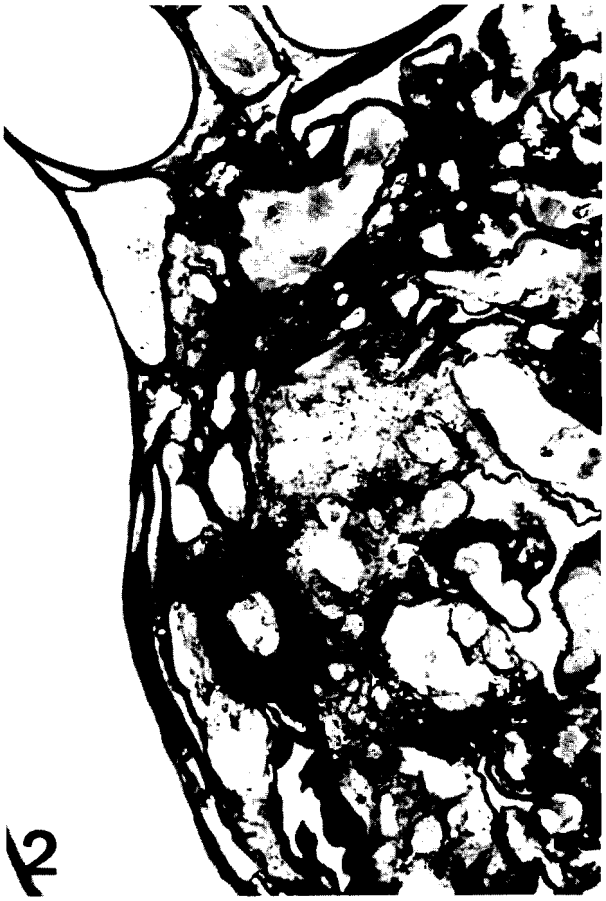

Fig. 2. Focal and segmental glomerulonephritis (F/S GN). Segmental increase of the mesangial area by the proliferation of mesangial cells. Silver-methenamine. × 1,000

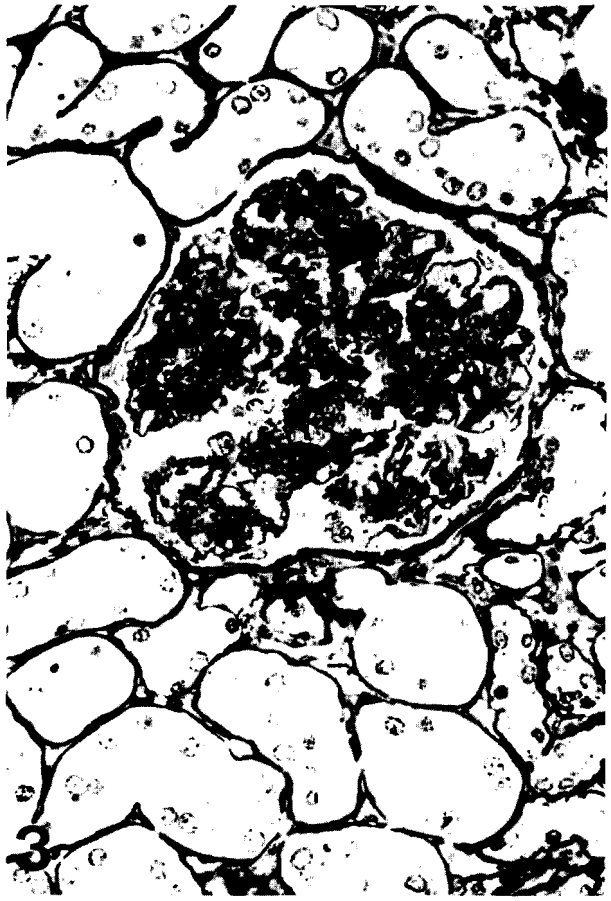

Fig. 3. Diffuse glomerulonephritis (Dif GN). Global increase in the mesangial area due to the deposit of argentophilic material. Silver-methenamine. × 400

Fig. 4. Membranous glomerulonephritis (Mem GN). Spikes in the basal membrane of the glomerular capillaries (asterisk) and sclerosis of the mesangium (arrows). Silver-methenamine. × 1,000

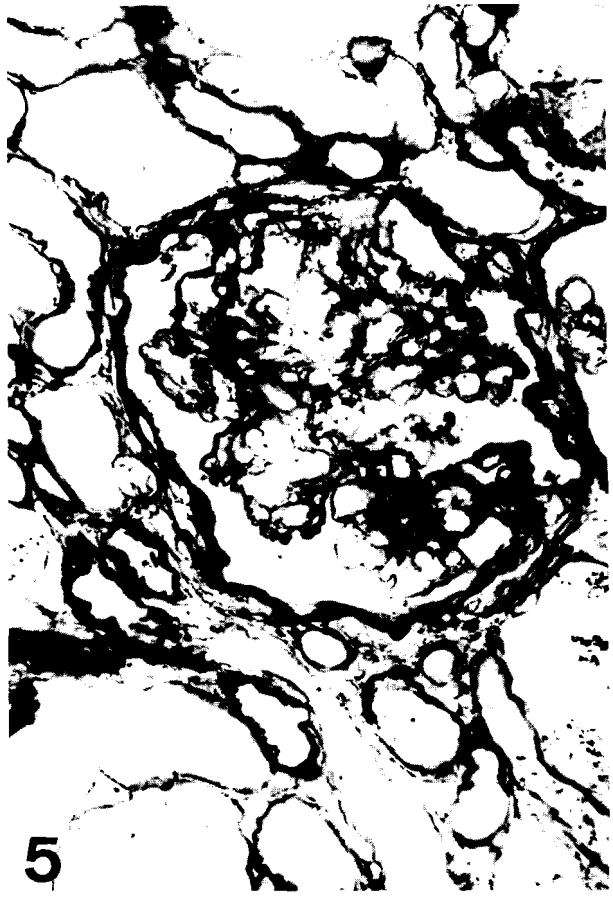

Fig. 5. Advanced sclerosing glomerulonephritis (Ad S GN). Abundant deposits of argentophilic material in the mesangium and sinquia between the capillaries turf Silver-methenamine. × 400

Table 1. Incidence of the different types of GN observed in relation to age and variety. (*) Age in months.

FORM OF GN	NUMBER	AGE(*)	VARIETY	
			WILD	STANDARD
Mes GN	13	4.1 ± 1.6	5	8
F/S GN	10	6.2 ± 2.5	6	4
Dif GN	10	6.7 ± 2.0	26	33
Mem GN	12	6.2 ± 3.1	4	8
Ad S GN	10	7.1 ± 2.6	2	8

Table 2. Incidence of different types of GN and interstitial plasmocytosis/periglomerular sclerosis associations.

GN	DOMINANT LESION	NUMBER	PASMOCYTOSIS		INTERS. SCLER.
			PERIVAS.	PERIGLOM.	
Mes GN (n = 13)	Mes. Scler.	3	0/*	**	0
	Mes. Prol.	10	0/*	**	0
F/S GN (n = 10)	Mes. Scler.	2	***	**	0/*
	Mes. Prol.	5	**	**	0
	Necrosis	3	**	*	0
Dif GN (n = 99)	Mes. Scler.	69	***	**	**
	Mes. Prol.	39	**	**	0
Mem GN (n = 12)	Mes. Scler.	8	***	*	0
	Spikes	4	**	0/*	*
Adv S GN (n = 10)	Glom. Scler.	10	***/****	**	***/****

0 = Wihout lesion; * = Slight lesion; ** = Moderate lesion; *** = Severe lesion; **** = Heavy diffuse lesion with tubular and glomerular damage.
n = number o GN; **Spikes:** spikes in capillary basement membrane; **Perivas:** perivascular lesion: **Periglom:** periglomerular lesion.

Partial necrosis of the capillary turf was identified by the loss of structure and local invasion of abundant neutrophil polimorphonuclears. The lesion was associated with necrotizing arteritis of the small diameter arteries of the kidney, heart, lung and brain.

Irregularly-distributed interstitial plasmocytosis was observed associated with F/S GN. Table 2 summarizes the distribution of this lesion.

Diffuse Glomerulonephritis (Dif GN)

Dif GN was observed in 99 cases, and two main forms of alteration could be identified: sclerosis of the mesangial area and proliferation of mesangial cells.

The sclerosis in the mesangial area was characterized by an increase in the area due to the amorphous deposit of argentophilic material (Fig. 3). In moderate Dif GN, the mesangial cells appeared easily identifiable and argentophilic deposits were noted in its cytoplasm.

When the lesion evolved towards more severe forms, the cells showed a small pyknotic nucleus, difficult to identify. The glomerular capillaries near to the vascular pole were seen to be totally or partially collapsed, and sometimes showed adherence (sinequias) between the distal capillary ends and the Bowman capsule. The Bowman space was smaller and serous liquid was occasionally observed in it. In severe Dif GN, the perimesangial basal membrane showed a great thickening in severe lesions and was very obvious in the vascular pole showing noticeable sclerosis when the glomerular lesions were considered severe.

69 cases were classified as Dif GN with a predominance of sclerosing lesions.

Dif GN with predominance of mesangial cell proliferation (30 cases) was characterized by the increase in the mesangial area, due to the increase in the number of cells. The lesions of capillary glomerular vessels noted were moderate, and consisted of a partial collapse of the same. Occasionally adherence of the vascular turf to the Bowman capsule was observed, always associated with severe lesions. The basal membrane of the capsule did not show any interesting modifications, the perimensangial basal membrane was noted to be thickened and occa-

Table 3. Quantitative analysis of different forms of GN

DETERMINATION	1	2	3
NORMAL GLOMERULUS			
Total glom. area	15822 ± 7067	15329 ± 5871	16193 ± 6179
Mesangial area	3054 ± 665	3176 ± 547	326 ± 426
Endothelial cells	13.8 ± 3.7	13.3 ± 2.6	14.8 ± 3.7
Mesangial cells	10.4 ± 1.4	11.0 ± 1.3	11.7 ± 1.6
Epithelial cells	18.8 ± 3.3	18.2 ± 3.3	17.6 ± 2.6
Total glom. cells	45.7 ± 14.0	46.1 ± 13.5	45.2 ± 12.0
Total glom. cells/1000μ^2	2.9 ± 1.0	3.1 ± 1.1	3.0 ± 0.9
Mesangial cells/1000μ^2	3.6 ± 0.8	3.4 ± 0.6	3.6 ± 0.6
Dif GN			
Total glom. area	17209 ± 3453	15828 ± 3714	16821 ± 36601
Mesangial area	7265 ± 327	7207 ± 298	7140 ± 206
Endothelial cells	12.7 ± 3.6	11.9 ± 3.9	12.4 ± 2.5
Mesangial cells	27.3 ± 8.5	26.3 ± 7.8	26.6 ± 8.0
Epithelial cells	24.9 ± 6.1	24.3 ± 6.5	24.6 ± 4.3
Total glom. cells	67.7 ± 16.2	67.4 ± 15.6	63.7 ± 16.2
Total glom. cells/1000μ^2	3.7 ± 0.3	3.9 ± 0.3	3.8 ± 0.4
Mesangial cells/1000μ^2	3.9 ± 0.7	3.9 ± 0.9	3.4 ± 0.4
Mes GN			
Total glom. area	15396 ± 5006	15355 ± 5237	15993 ± 6021
Mesangial area	5520 ± 372	5720 ± 320	5337 ± 411
Endothelial cells	13.6 ± 2.6	13.6 ± 2.6	14.0 ± 3.2
Mesangial cells	13.0 ± 2.1	13.2 ± 2.1	12.8 ± 2.9
Epithelial cells	19.1 ± 2.7	18.7 ± 2.9	20.6 ± 3.0
Total glom. cells	47.6 ± 10.0	46.9 ± 11.2	46.1 ± 14.0
Total glom. cells/1000μ^2	3.5 ± 1.6	3.2 ± 1.3	2.7 ± 1.7
Mesangial cells/1000μ^2	2.6 ± 1.1	2.8 ± 8.0	2.2 ± 1.3
Mem G			
Total glom. area	23115 ± 3775	21670 ± 4370	19873 ± 4369
Mesangial area	6252 ± 1708	6401 ± 1856	6124 ± 1536
Endothelial cells	15.2 ± 3.6	16.1 ± 3.9	14.9 ± 3.2
Mesangial cells	11.0 ± 5.0	11.6 ± 5.3	12.3 ± 4.1
Epithelial cells	22.8 ± 6.5	23.1 ± 6.8	23.0 ± 6.1
Total glom. cells	48.0 ± 12.8	51.3 ± 11.3	51.9 ± 5.6
Total glom. cells/1000μ^2	2.2 ± 0.4	1.8 ± 0.7	2.1 ± 0.6
Mesangial cells/1000μ^2	3.7 ± 0.5	4.1 ± 0.4	4.0 ± 0.5
Adv. S GN			
Total glom. area	11376 ± 2639	10831 ± 2379	10930 ± 2754
Mesangial area	7194 ± 723	7058 ± 801	7025 ± 780
Endothelial cells	6.4 ± 1.3	5.1 ± 1.0	6.2 ± 1.1
Mesangial cells	5.9 ± 2.0	5.8 ± 2.4	5.9 ± 1.8
Epithelial cells	13.0 ± 3.2	12.6 ± 2.9	13.1 ± 3.0
Total glom. cells	24.0 ± 5.7	23.7 ± 4.9	24.1 ± 4.3
Total glom. cells/1000μ^2	1.8 ± 0.4	1.7 ± 0.3	0.9 ± 0.2
Mesangial cells/1000μ^2	0.9 ± 0.2	0.9 ± 0.4	0.9 ± 0.2

1. First observation, **2.** Objectivity test. **3.** Repetitivity test.

Table 4. Statistical analysis of morphometric parameters in different GN in comparison with normal values.

DETERMINATION	Mes GN	Dif GN	Mem GN	Adv. S GN
Total glom. area	0	0	***	***
Mesangial area	**	***	**	***
Endothelial cells	**	***	***	***
Mesangial cells	**	***	0	***
Epithelial cells	0	*	**	***
Total glom. cells	0	**	**	**
Total glom. cells/100μ^2	0	**	0	***
Mesangial cells/100μ^2	***	0	0	***

0 Without differences, *p < 0.01, **p < 005, ***p < 0.001

sionally spikes were identified in the capillary basal membranes. Intracapillary, some polymorphonuclear neutrophils were found adhering to the vascular endothelium.

30 cases were classified as Dif GN with predominance of mesangial cell proliferation. The interstitial plasmocytosis associated with the various types of lesion is summarized in Table 2.

Membranous Glomerulonephritis (Mem GN)

The most interesting alterations in this form of GN were located in the basal membrane of the glomerular capillaries and the centre of the mesangium.

The basal membrane of the capillaries was moderately thickened and showed various argentaffin prolongations like spikes that protruded between the glomerular podocytes. These spikes have been observed in all the positions of the vascular pole. The centre of the mensagium was modified in moderate cases, but a certain amount of mesangial sclerosis was noted in severe Mem GN (Fig. 4).

Mem GN was diagnosed in 12 animals, 8 of which showed mesangial sclerosis as well as spikes. The associated interstitial plasmocytosis can be studied in Table 2.

Advanced Sclerosing Glomerulonephritis (Adv S GN)

Adv S GN was observed in 10 cases. The principal changes observed consisted of severe sclerosis in the vascular mass, with a loss of structure and collapse of the capillary vessels. Abundant deposits of argentophilic and PAS-positive material were noted in the mesangial area, which was dilated and poor in cells. Also, numerous adhesions were noted between the Bowman capsule and the capillary turf (Fig. 5).

The interstitial plasmocytosis observed was massive and is summarized in Table 2. A fibrous tissue often surrounded the glomerules, specially when the glomerular sclerosis was considered severe.

Quantitative study

The results obtained in the quantitative analysis of the lesions are summarized in Table 3 for each of the main observations (100% of the samples). The repetitivity test was valid in 95% of observations and objectivity in 99% of the same, using the Stundent «t» test as method of comparison.

Table 4 gives a comparative study of the results obtained for normal glomerules and for the various types of GN, allowing the degree of ateration to be recognized and also the participation of the various elements analyzed in the lesion.

Discussion

Our work classified the various glomerular lesions observed in the AD of mink spontaneously infected according to the WHO standards. We recognised 5 principal forms of GN: Mes GN (n=13); F/S GN (n=10); Dif GN (n=99;) Mem GN (n=12); and Adv S GN (n=10), with an incidence similar to that described Churg and Sobin (1982) in Systemic Lupus Erytematous nephyritis in man. However, note should be taken of the uniformity of the glomerular lesions in the infected animals, contrary to what occurs in man where the intensity of the lesion varies between different glomerules and renal lobules.

The glomerular lesions occurring in the course of AD were classified within GN according to the deposit of circulating immunocomplexes (IC) and is therefore intimately related to the IC levels in the blood (Henson et al., 1969; Muller-Peddinhaus and Trautwein, 1983; Porter et al., 1984).

The minks infected with AD virus which developed the disease progressively, showed hypergammaglobulinemia two weeks after infection (Porter et al., 1984). The IC deposits began to be visible using electron microscope techniques three weeks after infection in the subendothelium and in the mesangial area (Henson et al., 1969). The IC entered these areas through the pores of the vascular endothelium or through certain defects in the capillary cover favoured by the presence of lymphocytes. Using an optical microscope, the IC deposits began to be visible between the 5th and 6th week post-infection (Trautwein and Seidler, 1972; Muller-Peddinhaus and Trautweir, 1983).

The lesions showing mesangial sclerosis were the most frequently noted during our study, either in segmental or global form, and were characterized by the deposit in the mesangial area of argentophilic material, responsible for the regressive images observed in the cells of the mesangium. Henson et al. (1967) explained this phenomenon by studying it by ultrastructural techniques; the deposit of macromolecular material would be excessive for the phagocytarial capacity of the mesangial cells, which, while they were initially active, later returned to a non-functioning state.

Other autors (Muller-Pedinhaus and, Trautwein, 1983) demonstrated that animals that develop this type of GN show a maximum IC level 7 weeks after the experimental infection, which slowly diminishes until the 13th post-infection week. The sclerosis lesion therefore developed as a consequence of a prolonged deposit of IC —or its products— in the renal glomerule. The Adv S GN is the most severe degree of lesion and represents advanced forms of glomerular lesions.

A certain mesangial sclerosis has been described associated with the age of the minks (Muller-Peddinhaus and Trautwein, 1983; Nieto et al., 1989), and other species of animals such as the rat and hamster (Gutman and Andersen, 1968; Course and Stilmant, 1975) and in man (Kawano et al., 1971). This alteration consists basically of a moderate increase in the mesangial area, without any important regressive phenomena being observed in the cells.

GN with proliferation of mesangial cells results, as in the previous lesion, from the stimulus provoked by the IC deposit in the glomerule (Henson et al., 1967); in minks infected with AD virus the IC level remained constant during the 7th to the 13th week post-infection (Muller-Pendinhaus and Trautwein, 1983). Various transition situations between the cellular proliferation and the mesangium sclerosis were noted in our study, which, together with the analysis of the age of the animals, allows us to suppose that the proliferating lesions developed initially, to a greater or lesser degree, and that later they evolved towards cellular regression and sclerosis due to the continuous effect of IC deposit.

Mem GN are easily identified from the appearance of subepithelial argentophilic spikes that may or may not be associated with a certain degree of mesangial sclerosis. Mem GN occur in animals that show small sized IC which can easily penetrate through the glomerule filter, depositing themselves between the epithelial cells and the capillary basal membrane (Muller-Peddinhaus and Trautwein, 1983).

F/S GN, with necrotizing lesions of the vascular turf, and infiltration of neutrophil polymorphonuclears, represents a severe glomerular lesion associated with strong immune responses against the infection by AD virus (Muller-Peddinhaus and Trautwein, 1983). The alteration would be provoked by massive IC deposit in the glomerule and its appearance would be associated with necrotizing arteritis of the small and medium diameter arteries (Churg and Sobin, 1983; Muller-Peddinhaus and Trautwein, 1983).

The quantiative analysis of glomerular lesions has been of great assistance both in the study of the pathogenesis of the lesion and in the identification of certain GN that morphologically are difficult to classify by other methods. The excellent results that have been obtained using metacrylate and silver-methenamine techniques allowed an easy identification in the quantitative analyses, which in our experience, were very high (99% and 95% respectively).

The conclusions of greatest interest for the diagnosis were those referring to the mesangial area and the number of mesangial cells. Important, and statistically significant differences as to those of normal glomerules were noted in the mesangial spaces of all the types of lesion described. The mesangial cells actively participate in the lesion, as is shown by the proliferation noted in Mes, F/S, Dif and Mem GN, regressing to an inactive state in Adv S GN, the terminal form of GN. The quantitative analysis also revealed the increase in the number of epithelial cells in Dif and Mem GN, which suggests the existence of a certain stimulus from the deposit which is only evident in moderate of severe lesions. This observation coincides partially with a certain type of GN described in the LES nephritis (Churg and Sobin, 1982).

The quantification of Adv S/GN shows important glomerular hypocellularity due to the gradual increase of the sclerosis.

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